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TITLE OF THE INVENTION (280 characters max)

NOVEL M3 MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

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ENCLOSED APPLICATION PARTS (check all that apply)

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PU60603P

Nov l M_3 Muscarinic Ac tylcholin R c ptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of cyclic amines, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

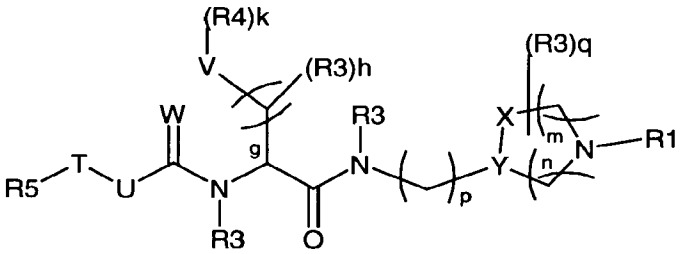
Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72

/id}{Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula I



(I)

wherein

When X and Y are carbons, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O, S, or NH;

U is NR3, O, or bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an integer from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: hydrogen, phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-

C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

SUMMARY OF THE INVENTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be

separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

The term "C_1-C_8 alkyl" and "C_1-C_6 alkyl" is used herein includes both straight or branched chain radicals of 1 to 6 or 8 carbon atoms. By example this term includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl and the like. "Lower alkyl" has the same meaning as C_1-C_8 alkyl.

Herein "C_1-C_8 alkoxy" includes straight and branched chain radicals of the likes of -O-CH_3, -O-CH_2CH_3, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.

"C_3-C_8-cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane, and the like.

"Halogen" or "halo" means F, Cl, Br, and I.

The preferred compounds of Formula I include those compounds wherein:

When X and Y are carbons, n is 1, or 2; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, and phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl,

unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl;wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6,

CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

Even more preferred are those compounds where:

X and Y are carbons;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, or 3;

T is selected from the group consisting of unsubstituted or substituted phenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals

selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

or a pharmaceutically acceptable salt.

The preferred compounds are selected from the group consisting of:

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate ;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-{[1-(phenylmethyl)-3-pyrrolidinyl]amino}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[4-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[4-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[3-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[3-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
N-[({4-[(ethylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;
N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide;
N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-(2-naphthalenylmethyl)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxo-1-{[4-(phenylcarbonyl)phenyl]methyl}ethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-{[4-(methyloxy)phenyl]methyl}-2-oxoethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)hexahydro-1*H*-azepin-3-yl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]hexahydro-1*H*-azepin-3-yl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate; and
Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
or a pharmaceutically acceptable salt.

The most preferred compounds are selected from the group consisting of:
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate; and

Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

or a pharmaceutically acceptable salt.

Methods of Preparation

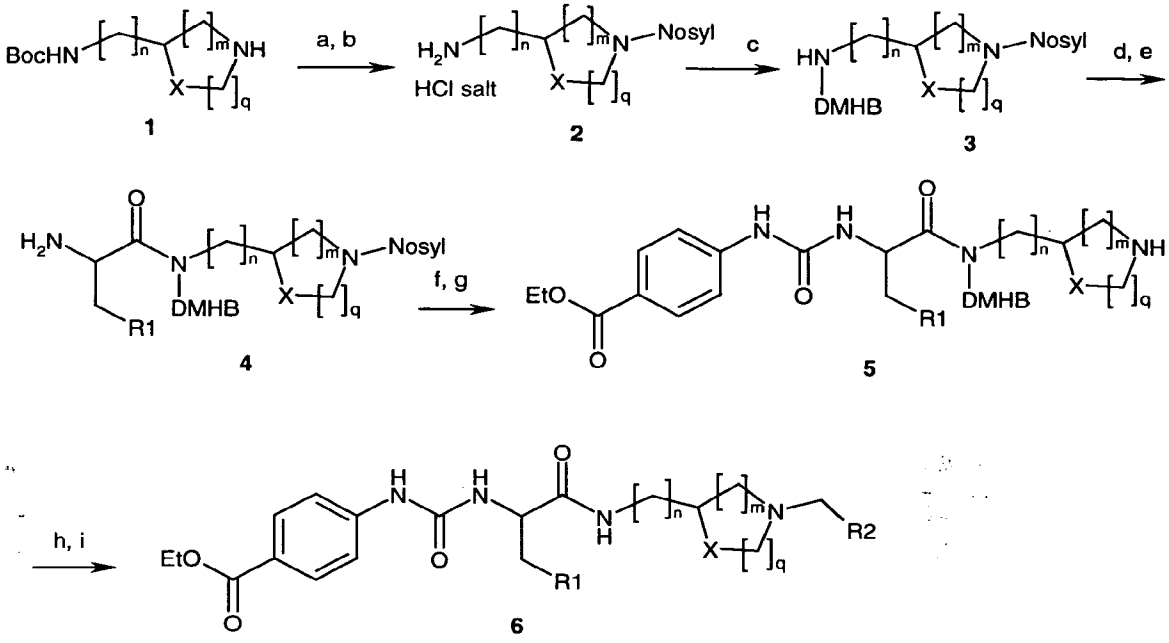
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1, R3, R4, R5 and R6, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

Resin-bound amines **3** were prepared by reductive alkylation of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with nosyl-protected diamine HCl salts **2**, which were prepared from Boc-protected diamines **1** (Scheme 1). Reactions of **3** with Fmoc protected amino acids, followed by removal of the protecting group, provided resin-bound intermediates **4**. Reactions of **4** with isocyanates afforded the corresponding resin-bound ureas, which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **5**. Reductive alkylation of **5** with aldehydes produced resin-bound tertiary amines, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **6**.

Scheme 1



Conditions: a) 2-nitrobenzenesulfonyl chloride (Nosyl-Cl), pyridine, CH_2Cl_2, 0 °C – rt; b) 4 M HCl in1,4-dioxane, MeOH, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), $Na(OAc)_3BH$, diisopropylethylamine, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; d) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; e) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; f) ethyl 4-isocyanatobenzoate, 1,2-dichloroethane, rt; g) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; h) R2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; i) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

Example 1

Preparation of Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

a) 3-Amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt

To a solution of 3-(*tert*-butoxycarbonyl-amino)pyrrolidine (20.12 g, 108 mmol) in 250 mL of anhydrous methylene chloride at 0 °C was added 13.1 mL (162 mmol) of anhydrous pyridine, followed by slow addition of 25.2 g (113.4 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt over 1 h and stirred at rt for 16 h. The mixture was poured into 300 mL of 1 M aqueous $NaHCO_3$ solution. After the resulting mixture was stirred at rt for 30 min, the organic layer was separated and washed with 500 mL of 1N aqueous HCl solution twice. The resulting organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next step without further purification.

To a mixture of the above residue in 140 mL of anhydrous MeOH was added 136 mL (544 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was stirred at rt for 16 h, concentrated *in vacuo* and further dried in vaccum oven at 35 °C for 24 h to yield 3-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt as a yellow solid (30.5 g, 92% over the two steps): ^1H NMR (400 MHz, d_6-DMSO) δ 8.63 (s, 3 H), 8.08-7.98 (m, 2 H), 7.96-7.83 (m, 2 H), 3.88-3.77 (m, 1 H), 3.66-3.56 (m, 2 H), 3.46-3.35 (m, 2 H), 2.28-2.16 (m, 1 H), 2.07-1.96 (m, 1 H).

b) DMHB resin-bound ethyl 4-[({[(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 10% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of example **1a** and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH_2Cl_2/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.98 g (4.30 mmol) of Fmoc-Try(tBu)-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.82 mL (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 657 $[M+H-tBu]^+$.

The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting

resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 435 [M+H-tBu]$^+$.

To a mixture of 200 mg (0.192 mmol, 0.959 mmol/g) of the above dry resin in 5 mL of anhydrous 1,2-dichloroethane was added 183.4 mg (0.959 mmol) of ethyl 4-isocyanatobenzoate. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 626 [M+H-tBu]$^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of 1-methyl-2-pyrrolidinone was added 265 mg (1.92 mmol) of K_2CO_3 and 0.0985 mL (0.96 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H_2O (3 x 10 mL), DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 441 [M+H-tBu]$^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 234 mg (1.918 mmol) of 4-hydroxybenzaldehyde and 407 mg (1.918 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h to yield DMHB resin-bound ethyl 4-[({[(1*S*)-

1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (0.192 mmol).

c) Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

The above dry resin (**1b**, 0.192 mmol) was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (white powder, 63 mg, 60% over 9 steps): MS (ESI) 547 $[M+H]^+$.

Proceeding in a similar manner, but replacing 3-(*tert*-butoxycarbonyl-amino)pyrrolidine with the appropriate Boc-protected diamines and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 1 - 10 were prepared.

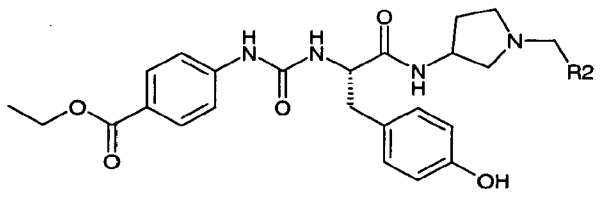


Table 1

Example	R2	MS $[M+H]^+$
2	3,4-methylenedioxy phenyl	575
3	4-fluoro phenyl	549
4	H	455
5	methyl	469
6	ethyl	483
7	propyl	497
8	butyl	511
9	pentyl	525
10	cyclohexyl	537
11	cyclopropyl	495
12	2-methylpropyl	511
13	phenyl	531
14	3-hydroxy phenyl	547
15	2-hydroxy phenyl	547
16	4-cyano phenyl	556
17	3-cyano phenyl	556
18	2-cyano phenyl	556
19	4-trifluoromethyl phenyl	599
20	3-trifluoromethyl phenyl	599
21	2-trifluoromethyl phenyl	599
22	4-chloro phenyl	565
23	3-chloro phenyl	565
24	2-chloro phenyl	565
25	3,4-chloro phenyl	599
26	3,4-dimethoxy phenyl	591
27	4-methoxy phenyl	561
28	3-methoxy phenyl	561

29	2-methoxy phenyl	561
30	4-hydroxy-3-methoxy phenyl	577
31	3-phenoxy phenyl	623
32	4-acetoamino phenyl	588
33	4-biphenyl	607
34	4-[3-(dimethylamino)propyl]oxy phenyl	632
35	quinolin-2-yl	582
36	4-N,N-dimethylamino phenyl	574
37	4-hydroxy-2-nitro phenyl	592
38	4-hydroxy-3-nitro phenyl	592
39	4-hydroxy-3,5-dimethoxy phenyl	607
40	4-(methyloxy)carbonyl phenyl	589
41	phenethyl	559
42	2-nitro phenyl	576
43	4-methyl-1*H*-imidazole-5-yl	535

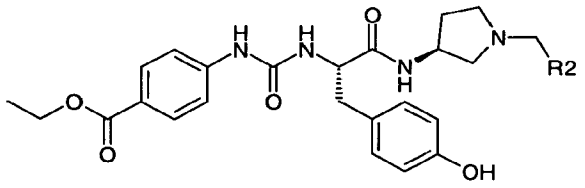


Table 2

Example	**R2**	**MS [M+H]$^+$**
44	4-hydroxy phenyl	547
45	4-fluoro phenyl	549
46	4-cyano phenyl	556
47	3,4-methylenedioxy phenyl	575
48	3,4-dimethoxy phenyl	591
49	cyclopropyl	495
50	3-hydroxy phenyl	547

51	3-fluoro phenyl	549
52	3-cyano phenyl	556
53	4-acetyl phenyl	573
54	4-acetamido phenyl	588
55	H	455
56	4-carboxy phenyl	575
57	4-chloro phenyl	565
58	3-chloro phenyl	565

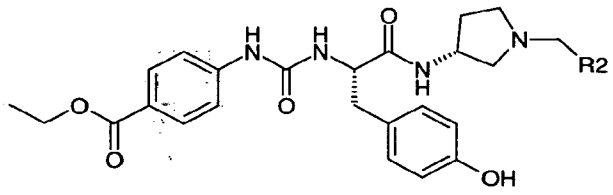


Table 3

Example	R2	MS $[M+H]^+$
59	4-hydroxy phenyl	547
60	4-fluoro phenyl	549
61	4-cyano phenyl	556
62	3,4-methylenedioxy phenyl	575
63	3,4-dimethoxy phenyl	591
64	cyclopropyl	495

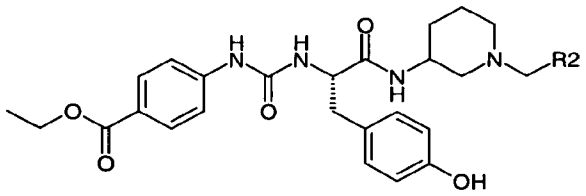


Table 4

Example	R2	MS $[M+H]^+$
65	4-hydroxy phenyl	561
66	4-fluoro phenyl	563
67	4-cyano phenyl	570
68	3,4-methylenedioxy phenyl	589
69	3,4-dimethoxy phenyl	605
70	cyclopropyl	509

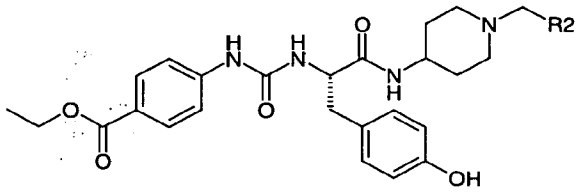


Table 5

Example	R2	MS $[M+H]^+$
71	4-hydroxy phenyl	561
72	4-fluoro phenyl	563
73	4-cyano phenyl	570
74	3,4-methylenedioxy phenyl	589
75	3,4-dimethoxy phenyl	605
76	cyclopropyl	509

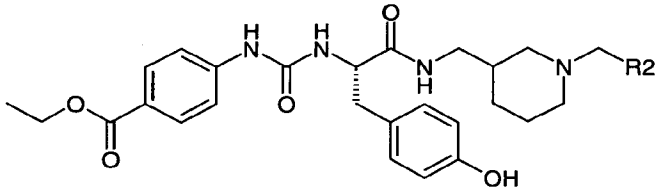


Table 6

Example	R2	MS $[M+H]^+$
77	4-hydroxy phenyl	575

78	4-fluoro phenyl	577
79	4-cyano phenyl	584
80	3,4-methylenedioxy phenyl	603
81	3,4-dimethoxy phenyl	619
82	cyclopropyl	523

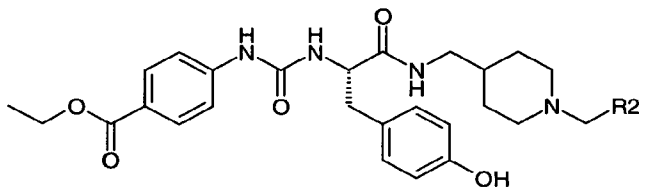


Table 7

Example	R2	MS $[M+H]^+$
83	4-hydroxy phenyl	575
84	4-fluoro phenyl	577
85	4-cyano phenyl	584
86	3,4-methylenedioxy phenyl	603
87	3,4-dimethoxy phenyl	619
88	cyclopropyl	523

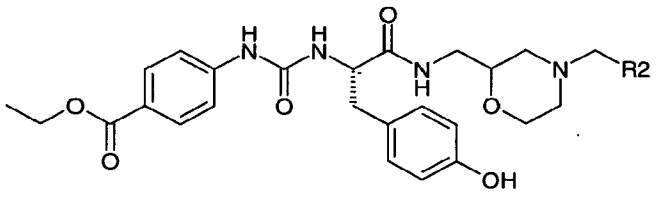


Table 8

Example	R2	MS $[M+H]^+$
89	4-hydroxy phenyl	577
90	4-fluoro phenyl	579
91	4-cyano phenyl	586
92	3,4-methylenedioxy phenyl	605

93	3,4-dimethoxy phenyl	621
94	cyclopropyl	625

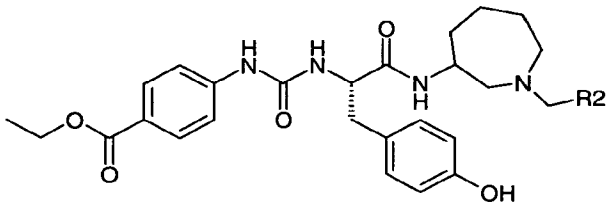
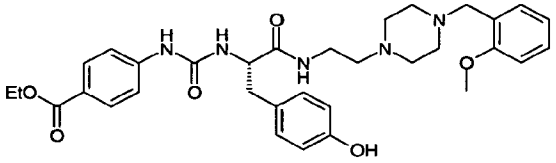


Table 9

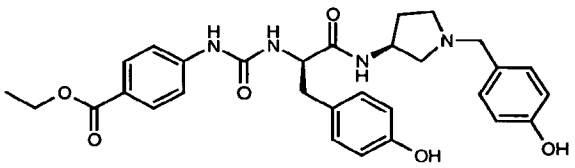
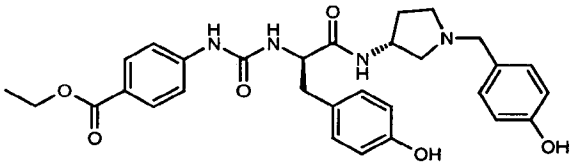
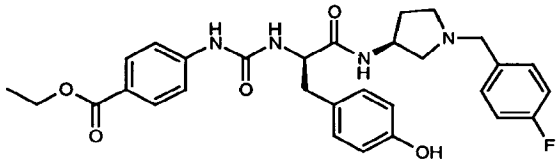
Example	R2	MS $[M+H]^+$
95	4-hydroxy phenyl	575
96	4-fluoro phenyl	577
97	4-cyano phenyl	584
98	3,4-methylenedioxy phenyl	603
99	3,4-dimethoxy phenyl	619
100	cyclopropyl	523

Table 10

Example	R2	MS $[M+H]^+$
101		604

Proceeding in a similar manner as described in example **1**, but replacing 3-(*tert*-butoxycarbonyl-amino)pyrrolidine with 3*S*-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine or 3*R*-(+)-(*tert*-butoxycarbonyl-amino)pyrrolidine, replacing Fmoc-Try(tBu)-OH with other Fmoc protected amino acids and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 11 - 14 were prepared.

Table 11

Example	Compounds	MS [M+H]$^+$
102		547
103		547
104		549

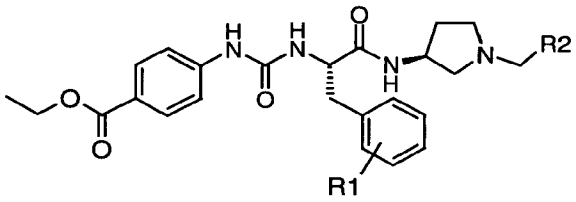


Table 12

Example	R1	R2	MS [M+H]$^+$
105	4-chloro	3,4-methylenedioxy phenyl	593
106	4-phenylcarbonyl	3,4-methylenedioxy phenyl	663
107	4-methoxy	3,4-methylenedioxy phenyl	589
108	4-fluoro	3,4-methylenedioxy phenyl	577
109	4-chloro	4-fluoro phenyl	567
110	4-phenylcarbonyl	4-fluoro phenyl	637
111	4-methoxy	4-fluoro phenyl	563
112	4-fluoro	4-fluoro phenyl	551
113	4-methyl	3,4-methylenedioxy phenyl	573

114	4-bromo	3,4-methylenedioxy phenyl	637
115	3,4-dichloro	3,4-methylenedioxy phenyl	627
116	3-chloro	3,4-methylenedioxy phenyl	593
117	4-cyano	3,4-methylenedioxy phenyl	584
118	2-chloro	3,4-methylenedioxy phenyl	593
119	4-trifluoromethyl	3,4-methylenedioxy phenyl	627
120	3,4-dimethoxy	3,4-methylenedioxy phenyl	619
121	4-methyl	4-fluoro phenyl	547
122	3-chloro	4-fluoro phenyl	567
123	4-cyano	4-fluoro phenyl	558
124	3-cyano	4-fluoro phenyl	558
125	3,4-dimethoxy	4-fluoro phenyl	593
126	4-amino	3,4-methylenedioxy phenyl	574
127	4-amino	4-fluoro phenyl	548

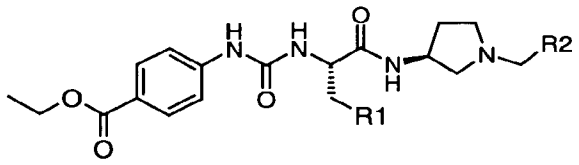


Table 13

Example	R1	R2	MS $[M+H]^+$
128	2-naphthyl	3,4-methylenedioxy phenyl	609
129	2-naphthyl	4-fluoro phenyl	583

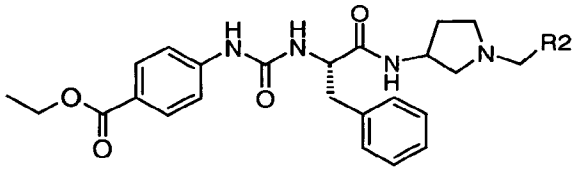


Table 14

Exampl	R2	MS $[M+H]^+$

130	2-methoxy phenyl	545
131	3,4-methylenedioxy phenyl	559

Proceeding in a similar manner as described in example **1**, but replacing ethyl 4-isocyanatobenzoate with the appropriate isocyanates and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 15 and 16 were prepared.

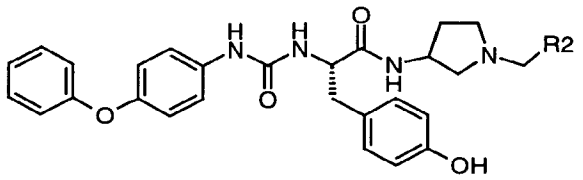
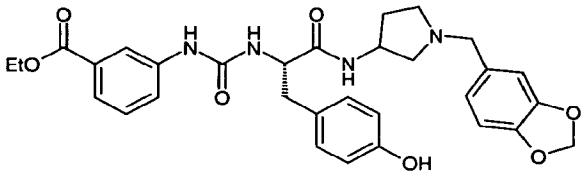


Table 15

Example	**R**	**MS [M+H]$^+$**
132	2-methoxy phenyl	581
133	3,4-methylenedioxy phenyl	595

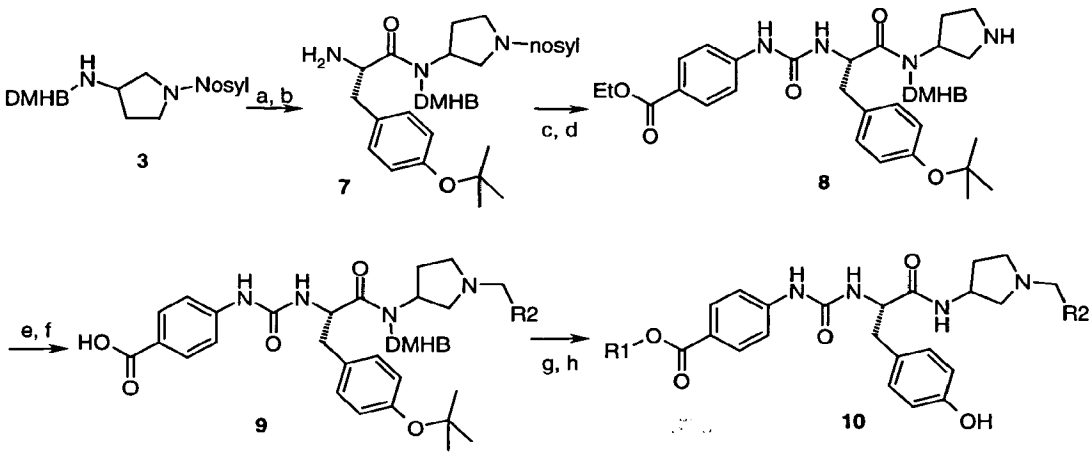
Table 16

Example	Compound	MS $[M+H]^+$
134		441

Preparation 2

Resin-bound amines **3** were prepared in the same way as described in preparation 1. Reactions of **3** with Fmoc-Try(tBu)-OH, followed by removal of the Fmoc protecting group, provided resin-bound intermediates **7**. Reactions of **7** with ethyl 4-isocyanatobenzoate afforded the corresponding resin-bound ureas, which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **8**. Reductive alkylation of **8** with appropriate aldehydes produced resin-bound tertiary amines, which were treated with potassium trimethylsilanolate (KOTMS) in tetrahydrofuran (THF) to give the corresponding carboxylic acids **9**. Acids **9** reacted with appropriate alcohols in presence of 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) and 1-methylimidazole (MeIm) to afford the corresponding esters, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to yield targeted compounds **10** (Scheme 2).

Scheme 2



Conditions: a) Fmoc-Try(tBu)-OH, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; b) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; c) ethyl 4-isocyanatobenzoate, 1,2-dichloroethane, rt; d) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; e) R2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) KOTMS, THF, rt; g) R1OH, MSNT, MeIm, dichloromethane, rt; h) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Example 135

Preparation of Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

a) DMHB resin-bound 4-[({[(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoic acid

To a mixture of 50 mg (0.04 mmol, 0.809 mmol/g) of example **1b** in THF (3 mL) was added potassium trimethylsilanolate (KOTMS) (0.27 g,

0.7 M in THF). The mixture was shaken at rt for 2 days and then the resin was washed with THF (1 x 2 mL), CH_2Cl_2 (3 x 2 mL), MeOH (3 x 2 mL) and CH_2Cl_2 (3 x 2 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 1 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 519 $[M+H-tBu]^+$.

b) Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

To a mixture of the above dry resin (**135a**, 0.04 mmol) in dichloromethane (2 mL) was added 1-methylimidazole (0.043 mL, 0.27 M in DCM), followed by 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) (119 mg, 0.2 M in DCM) and 1-propanol (0.06 mL, 0.4 M in DCM). After the resulting mixture was shaken at rt for 24 h, the resin was washed with DCM (3 x 5 mL), CH_2Cl_2/MeOH (1:1, 3 x 5 mL) and MeOH (3 x 5 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (white powder, 6 mg, 27% over 11 steps): MS (ESI) 561 $[M+H]^+$.

Proceeding in a similar manner as described in example **135**, but replacing 1-propanol with the appropriate alcohols and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Table 17 were prepared.

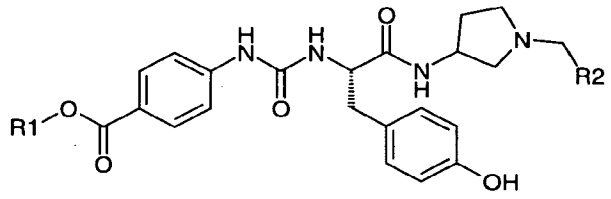


Table 17

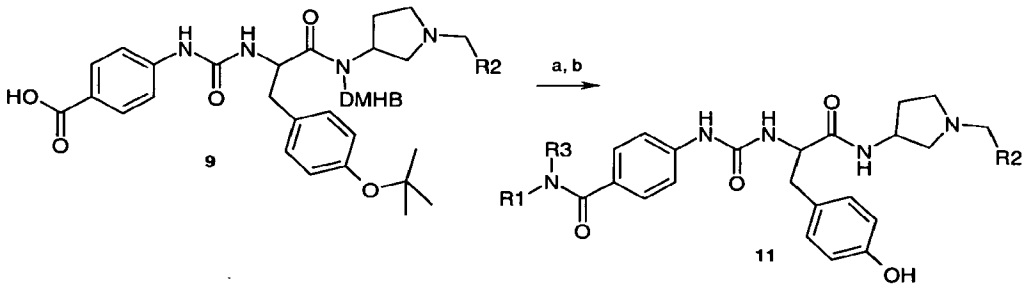
Example	R1	R2	MS $[M+H]^+$
136	methyl	4-hydroxy phenyl	533
137	n-pentyl	4-hydroxy phenyl	589
138	1-methylethyl	4-hydroxy phenyl	561
139	2-methylpropyl	4-hydroxy phenyl	575
140	2,2-dimethylpropyl	4-hydroxy phenyl	589
141	cyclopropylmethyl	4-hydroxy phenyl	573
142	cyclohexyl	4-hydroxy phenyl	601
143	cyclohexylmethyl	4-hydroxy phenyl	615
144	benzyl	4-hydroxy phenyl	609
145	2-phenylethyl	4-hydroxy phenyl	623
146	2-naphthyl	4-hydroxy phenyl	645
147	4-(1,1-dimethylethyl)phenyl	4-hydroxy phenyl	651
148	1-naphthyl	4-hydroxy phenyl	645
149	2-(1-naphthyl)ethyl	4-hydroxy phenyl	673
150	4-biphenyl	4-hydroxy phenyl	671
151	2,2-diphenylethyl	4-hydroxy phenyl	699
152	3,3-diphenylpropyl	4-hydroxy phenyl	713

153	methyl	4-cyano phenyl	542
154	n-propyl	4-cyano phenyl	570
155	n-pentyl	4-cyano phenyl	598
156	1-methylethyl	4-cyano phenyl	570
157	2-methylpropyl	4-cyano phenyl	584
158	2,2-dimethylpropyl	4-cyano phenyl	598
159	cyclopropylmethyl	4-cyano phenyl	582
160	cyclohexyl	4-cyano phenyl	610
161	2-phenylethyl	4-cyano phenyl	632
162	2-(1-naphthyl)ethyl	4-cyano phenyl	682

Preparation 3

Resin-bound acids **9** were prepared in the same way as described in preparation 2. Reactions of acids **9** with appropriate amines in presence of PyBOP and diisopropylethyl amine (DIEA) afforded the corresponding amides, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **11** (Scheme 3).

Scheme 3



Conditions: a) (R1)(R3)NH, PyBOP, diisopropylethyl amine, 1-methyl-2-pyrrolidinone, rt; b) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Example 163

Preparation of *N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide

To a mixture of example **135a** (0.04 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added PyBOP (0.31 g, 0.3 M in 1-methyl-2-pyrrolidinone), followed by 1-propylamine (0.2 mL, 1.2 M in 1-methyl-2-pyrrolidinone) and diisopropylethyl amine (0.21 mL, 0.6 M in 1-methyl-2-pyrrolidinone). After the resulting mixture was shaken at rt for 24 h, the resin was washed with DCM (3 x 5 mL), CH_2Cl_2/MeOH (1:1, 3 x 5 mL) and MeOH (3 x 5 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2 h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide (white powder, 12 mg, 54% over 11 steps): MS (ESI) 560 $[M+H]^+$.

Proceeding in a similar manner as described in example **163**, but replacing 1-propylamine with the appropriate amines and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Table 18 were prepared.

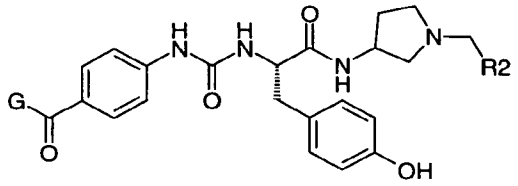


Table 18

Example	G	R2	MS [M+H]$^+$
164	1-propylamino	4-fluoro phenyl	562
165	1-propylamino	2-methoxy phenyl	574
166	1-propylamino	2-phenylethyl	572
167	1-propylamino	3,4-methylenedioxy phenyl	588
168	1-propylamino	4-cyano phenyl	569
169	methylamino	4-hydroxy phenyl	532
170	ethylamino	4-hydroxy phenyl	546
171	1-butylamino	4-hydroxy phenyl	574
172	1-pentylamino	4-hydroxy phenyl	588
173	1-hexylamino	4-hydroxy phenyl	602
174	diethylamino	4-hydroxy phenyl	574
175	di-(n-propyl)amino	4-hydroxy phenyl	602
176	1-methylethylamino	4-hydroxy phenyl	560
177	2-methylpropylamino	4-hydroxy phenyl	574
178	cyclopropylamino	4-hydroxy phenyl	558
179	cyclopropylmethylamino	4-hydroxy phenyl	572
180	cyclohexylamino	4-hydroxy phenyl	600
181	piperidinyl	4-hydroxy phenyl	586
182	pyrrolidinyl	4-hydroxy phenyl	572
183	morpholinyl	4-hydroxy phenyl	588
184	phenylamino	4-hydroxy phenyl	594
185	benzylamino	4-hydroxy phenyl	608

186	2-phenylethylamino	4-hydroxy phenyl	622
187	[4-(2,3-dihydro-1H-indol-1-ylmethyl)phenyl]amino	4-hydroxy phenyl	620
188	methylamino	4-cyano phenyl	541
189	ethylamino	4-cyano phenyl	555
190	1-butylamino	4-cyano phenyl	583
191	1-pentylamino	4-cyano phenyl	597
192	1-hexylamino	4-cyano phenyl	611
193	diethylamino	4-cyano phenyl	583
194	di-(n-propyl)amino	4-cyano phenyl	611
195	1-methylethylamino	4-cyano phenyl	569
196	2-methylpropylamino	4-cyano phenyl	583
197	cyclopropylamino	4-cyano phenyl	567
198	cyclopropylmethylamino	4-cyano phenyl	581
199	cyclohexylamino	4-cyano phenyl	609
200	cyclohexylmethylamino	4-cyano phenyl	623
201	piperidinyl	4-cyano phenyl	595
202	pyrrolidinyl	4-cyano phenyl	581
203	morpholinyl	4-cyano phenyl	597
204	phenylamino	4-cyano phenyl	603
205	benzylamino	4-cyano phenyl	617
206	2-phenylethylamino	4-cyano phenyl	631
207	[4-(2,3-dihydro-1H-indol-1-ylmethyl)phenyl]amino	4-cyano phenyl	629

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25

ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described . CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM NaH CO_3, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium

levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (n = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine . Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

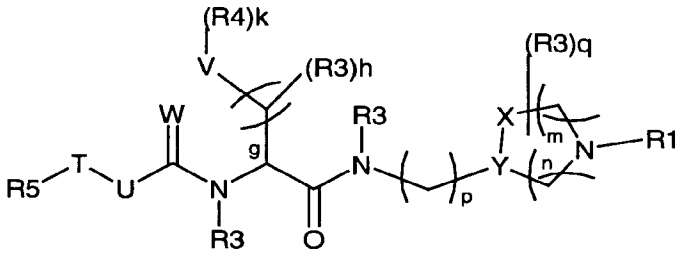
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention

to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula I herein below:



(I)

wherein

When X and Y are carbons, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O, S, or NH;

U is NR3, O, or bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an integer from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a

group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: hydrogen, phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl,

benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

2. A compound according to claim 1 consisting of the group selected from:

When X and Y are carbons, n is 1, or 2; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, or phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of

C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl,

pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

3. A compound according to claim 1 consisting of the group selected from:

X and Y are carbons;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, or 3;

T is selected from the group consisting of unsubstituted or substituted phenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy,

halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, or C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl,

benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

or a pharmaceutically acceptable salt.

4. A compound according to claim 1 selected from the group consisting of:

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate ;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-{[1-(phenylmethyl)-3-pyrrolidinyl]amino}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[4-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[4-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[3-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[3-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
N-[({4-[(ethylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;
N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;
N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-(2-naphthalenylmethyl)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxo-1-{[4-(phenylcarbonyl)phenyl]methyl}ethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-{[4-(methyloxy)phenyl]methyl}-2-oxoethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)hexahydro-1*H*-azepin-3-yl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]hexahydro-1*H*-azepin-3-yl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate; and
Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
or a pharmaceutically acceptable salt.

5. A compound according to claim 1 selected from the group consisting of:
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[({(1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate; and
Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
or a pharmaceutically acceptable salt.

6. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. A method according to claim 9 wherein administration is via inhalation via the mouth or nose.

11. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

12. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.

13. A method according to claim 12 wherein the compound has a duration of action of 24 hours or more.

14. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

ABSTRACT OF THE DISCLOSURE

Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.